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The Prognostic Significance of Multiple Station N2 in Patients with Surgically Resected Stage IIIA N2 Non-small Cell Lung Cancer

Mediastinal (N2) lymph node involvement is heterogeneous with huge variation in the extent and grouped together under stage IIIA. However, they showed a different survival even in the same stage. We tried to determine the prognostic implication of the multiple station N2 lymph node metastasis in stage IIIA N2 non-small cell lung cancer (NSCLC). The survival of stage IIIA N2 was analyzed according to the number of N2 station and their survival was compared with that of stage IIIB. In stage IIIA N2 NSCLC, multivariate analysis indicated that multiple station N2 was one of the independent prognostic factors for poor survival. The 5-yr survival of multiple station N2 IIIA (20.4%) was lower than that of single station N2 IIIA (33.8%) significantly ($p=0.016$), but when it was compared with that of stage IIIB (15.5%), there was no difference. Therefore, we suggest that multiple station N2 should be considered similar to stage IIIB disease with regard to predicting survival and accordingly should receive a new position in the TNM staging system.

Key Words : Lung Neoplasms; Lymph Node, Neoplasm Metastasis; Prognosis

Jin Gu Lee, Chang Young Lee,
In Kyu Park, Dae Joon Kim,
Sang Ho Cho, Kil Dong Kim*,
and Kyung Young Chung

Department of Thoracic and Cardiovascular Surgery,
Yonsei University College of Medicine, Seoul;
Department of Thoracic and Cardiovascular Surgery*,
Eulji University School of Medicine, Daejeon, Korea

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Address for correspondence

Kyung Young Chung, M.D.
Department of Thoracic and Cardiovascular Surgery,
Yonsei University College of Medicine, 134
Sinchon-dong, Seodaemun-gu, Seoul 120-752, Korea
Tel : +82.2-2228-2140, Fax : +82.2-393-6012
E-mail : kychu@yuhs.ac

INTRODUCTION

Nodal involvement is the most important prognostic factor in determining survival for patients with non-small cell lung cancer (NSCLC) (1, 2). However, conventional lymph node (LN) staging does not effectively reflect the wide differences in LN involvement and patient survival, even in patients classified within the same LN stage (3, 4). Furthermore, the characteristics of the mediastinal node (N2) are rather heterogeneous. Consequently, several subclassifications with regard to LN involvement have been proposed. Some investigators have also postulated the possible classification of a subgroup of multiple station N2 patients who have more unfavorable results compared to single station N2 patients with stage IIIA N2 NSCLC (3, 5-7).

In this retrospective study, we attempted to clarify the prognostic significance of multiple station N2 patients with stage IIIA N2 lung cancer and to propose an adequate TNM staging position for multiple station N2 disease by comparing the survival of multiple station N2 patients to the survival patients with stage IIIB disease.

MATERIALS AND METHODS

Between 1990 and 2005, 1,326 patients underwent operations for non-small cell lung cancer at our institution. Of these

patients, 430 patients were diagnosed with either stage IIIA N2 or stage IIIB disease by pathological examination. Patients who received preoperative induction therapy ($n=55$) and those who died within 1-month postoperatively ($n=17$) were excluded from our study. Ultimately, a total of 358 patients were analyzed retrospectively. All patients underwent a thoracic computed tomography (CT) scan. Clinical staging was determined by bronchoscopy, chest CT, abdominal ultrasonogram, and bone scans. Lymph nodes with a shortest diameter of 10 mm or more were considered enlarged. The mediastinal node status was assessed according to the system defined by Mountain and Dresler (8). Systematic node dissection of the both hilar and mediastinal lymph nodes was performed in all patients except for in 14 open and closure cases and 2 wedge resection cases. Six cycles of cisplatin-based adjuvant chemotherapy were considered for all patients with stage II through stage III from the early 1990s to 2004. After 2005, four cycles of adjuvant chemotherapy were considered. Postoperative radiotherapy was considered for patients who had N2-positive and those who had positive resection margin. A Multiple station N2 was defined as lymph node metastasis involving more than one N2 station. Skip N2 was defined as metastasis-free hilar and intrapulmonary lymph nodes. The pathological staging was based on the 1997-TNM classification system (9).

The group was comprised of 75 female and 283 male patients, with a median age of 61 yr (range, 31 to 78 yr). 262 patients were classified with stage IIIA N2 disease and 96

patients were classified with stage IIIB disease. Among the stage IIIB patients, 14 patients were open and closure cases. Of these 14 patients, 10 cases did not have a proven pathological node stage. The median follow-up duration was 18.5 months (range, 1.2 to 184.2 months). All patients were followed up until either death or the last follow-up date (December 31, 2006). The patient characteristics are summarized in Table 1.

The clinicopathological records of each patient with stage IIIA N2 disease were examined for prognostic factors such as age, sex, right or left side, type of surgical procedure (pneumonectomy or other procedure), histology, adjuvant chemotherapy, tumor location (upper or lower), T stage, metastatic node station (single or multiple station), and distribution of metastatic nodes (skip N2 or non skip N2). The survival rates of patients with stage IIIA N2 disease according to

significant prognostic factors were compared with those of patients with stage IIIB disease. The Institutional Review Board granted us permission to retrospectively review and publish the patient records.

Statistical analysis

The association between variables was analyzed by either chi-square or analysis of variances (ANOVA) tests. The duration of survival was defined as the interval between the date of surgery and either the date of death or the last follow-up date. Survival rates were calculated using the Kaplan-Meier method, and univariate analyses were performed using the log-rank test. Multivariate analyses were performed by means of the Cox proportional hazard model in variables that had *p* values less than 0.05 as determined by univariate analyses. A *p* value less than 0.05 was considered significant.

Table 1. Clinical and pathological patient characteristics

Variables	No. of patients (%)
Age (median)	61 (31-78)
Sex	
Male	283 (79.1)
Female	75 (20.9)
Type of resection	
Pneumonectomy	187 (52.2)
Bilobectomy	45 (12.6)
Lobectomy	110 (30.7)
Other*	16 (4.5)
Histological subtype	
Squamous cell	172 (48.0)
Adenocarcinoma	154 (43.0)
Other†	32 (9.0)
Pathologic tumor factor (pT)	
pT1	38 (10.6)
pT2	166 (46.4)
pT3	72 (20.1)
pT4	82 (22.9)
Pathologic node factor (pN)‡	
pN0	26 (7.3)
pN1	14 (3.9)
pN2	292 (81.6)
pN3	16 (4.5)
Stage	
IIIA	262 (73.2)
IIIB	96 (26.8)
N2 status in stage IIIA	
Single N2 station	175 (66.8)
Multiple N2 station	87 (33.2)
Skip N2 in stage IIIA	
Skip N2	97 (37.0)
Non-skip N2	165 (63.0)

*, Wedge resection in 2 patients and open and closure cases in 14 patients; †, large cell in 12, adenosquamous cell in 11, sarcomatoid carcinoma in 3 and neuroendocrine tumor in 5; ‡, 10 open and closure cases did not prove a pathological node factor.

Table 2. Prognostic factors in stage IIIA N2 patients by univariate analysis

Variables	No. of patients	5-yr survival rate (%)	<i>p</i> value
Age (yr)			0.000
≤60	122	37.6	
>60	140	21.4	
Sex			0.023
Male	206	25.6	
Female	56	41.6	
Side			0.228
Right	160	22.3	
Left	102	37.7	
Operation			0.017
Pneumonectomy	141	22.3	
Lobectomy or bilobectomy	121	37.7	
Adjuvant chemotherapy			0.000
Yes	162	37.7	
No	100	22.3	
Histology			0.933
Adenocarcinoma	111	29.3	
Others	151	28.8	
Location			0.588
Upper	132	29.2	
Middle or lower lobes	130	28.8	
T stage			0.029
T1-2	194	32.4	
T3	68	19.6	
Clinical N status			0.012
cN0-1	116	36.0	
cN2	146	23.6	
Number of metastatic N2 stations			0.016
Single	175	33.8	
Multiple	87	20.4	
Skip N2			0.647
Non-skip	165	30.1	
Skip	97	27.3	

RESULTS

Overall survival rate

The overall 5-yr survival rates were 29.1% (95% confidence interval [CI], 23.6 to 34.6%) for patients with stage IIIA

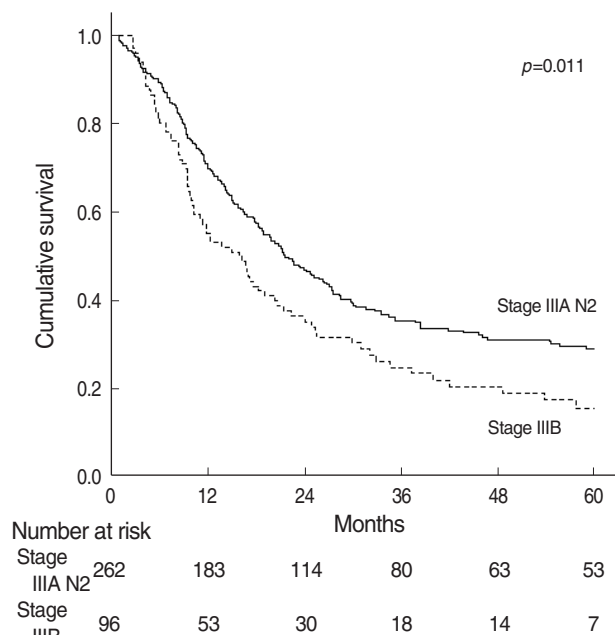


Fig. 1. Overall survival curves of patients with stage IIIA N2 and stage IIIB NSCLC.

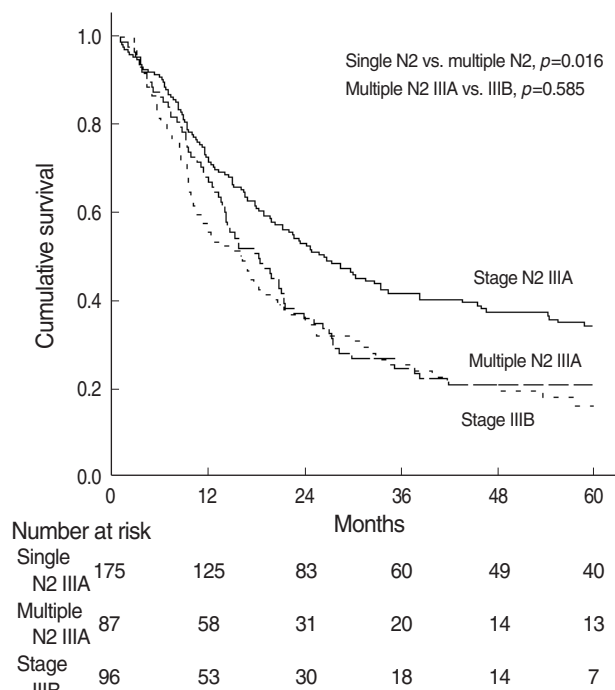


Fig. 2. Overall survival curves of patients with single station N2, multiple station N2, and stage IIIB NSCLC.

N2 disease and 15.5% (95% CI, 8.3 to 22.7%) for patients with stage IIIB disease, with median survival durations of 21.6 months (95% CI, 17.5 to 25.6 months) and 15.8 months (95% CI, 11.0 to 20.6 months), respectively. This difference in survival rates between the two patient groups was statistically significant ($p=0.011$) (Fig. 1).

Prognostic significance of multiple station N2 in patients with Stage IIIA N2 NSCLC

In stage IIIA N2 NSCLC, a univariate analysis using the variables listed in Table 2 showed that the following factors were significantly associated with poor outcome: age >60, male, T3 factor, pneumonectomy, clinical N2, no adjuvant chemotherapy, and multiple station N2. Using multivariate analysis, we found that the independent unfavorable prognostic factors were age >60, no adjuvant chemotherapy, and multiple station N2 (Table 3).

Survival rate according to the number of metastatic N2 stations

We evaluated the effect of the number of metastatic N2 stations upon stage IIIA patient survival. The overall 5-yr survival rates were 33.8% (95% CI, 26.8 to 40.8%) in single station N2 patients and 20.4% (95% CI, 13.3 to 27.5%) in multiple station N2 patients. The median survival times in single station N2 and multiple station N2 patients were 26.4 months (95% CI, 20.3 to 32.5 months) and 18.2 months (95% CI, 12.8 to 23.6 months), respectively. The difference was statistically significant ($p=0.016$). Furthermore, the survival rate of multiple station N2 patients in stage IIIA was compared with the survival rate of stage IIIB patients, and

Table 3. Prognostic factors in N2 IIIA patients as determined by Multivariate analysis

Variables	Hazard ratio	95% confidence interval	<i>p</i> value
Age (yr)			
Age>60/age≤60	1.620	1.204-2.180	0.001
Sex			
Male/female	1.320	0.907-1.921	0.147
Operation			
Pneumonectomy/Lobectomy or bilobectomy	1.328	0.976-1.807	0.071
Adjuvant chemotherapy			
Yes/no	0.568	0.425-0.759	0.000
T stage			
T3/T1-2	1.246	0.901-1.724	0.183
Clinical N status			
cN2/cN0-1	1.204	0.885-1.637	0.238
Number of metastatic N2 stations			
multiple/single	1.459	1.084-1.963	0.013

we found no significant difference ($p=0.585$) (Fig. 2).

Among the three groups, we found no difference in clinicopathological variables such as age, sex, histopathology, tumor size, number of resected LNs, or type of procedure performed (except for the 14 open and closure cases).

DISCUSSION

Our results indicate that the multiple station N2 criteria was one of the most important prognostic factors for poor outcome after surgery in patients with stage IIIA N2 NSCLC. Furthermore, we found that the multiple station N2 patients with stage IIIA had a survival rate that was similar to the stage IIIB patient survival rate.

Several factors, such as the clinical N2 factor, the number of metastatic N2 stations, T factor, tumor location, and skip N2, have been reported as important prognostic factors in patients with stage IIIA N2 cancer (7, 8, 10-13). Our univariate analysis study showed that the significant unfavorable prognostic factors were age >60, male, T3 factor, pneumonectomy, clinical N2, no history of adjuvant chemotherapy, and multiple station N2. Tumor location, histology, and skip N2 status showed no prognostic significance in this study. Furthermore, multivariate analysis confirmed that multiple station N2, age >60, and no history of adjuvant chemotherapy were significant, unfavorable prognostic factors. Several studies have shown that the number of metastatic mediastinal LNs was an important prognostic factor (14-16). Vansteenkiste and associates (17) reported that the 5-yr survival for patients with single station N2 was 29.6% versus 20.8% for those with multiple station N2 ($p=0.008$). In our study, the overall 5-yr survival rates were 33.8% in patients with single station N2 and 20.4% in patients with multiple station N2 ($p=0.016$). Besides the number of the metastatic mediastinal LNs, the clinical N factor and skip metastasis have also been considered prognostic factors in nodal factors (13, 17). In our study, patients with skip metastasis did not gain a survival benefit. In addition, clinical N2 patients showed significantly unfavorable clinical outcomes on univariate analysis but did not show a survival difference on to multivariate analysis. With these results, the number of the involved mediastinal LN stations can be recognized as a single and reliable finding that indicates highly advanced N2 lung cancer. The role of adjuvant chemotherapy is considered controversial, but recent clinical trials have begun to demonstrate the survival benefit of adjuvant chemotherapy in select cases of NSCLC patients. Recent guidelines generally recommend adjuvant chemotherapy for patients with completely resected stage IB through stage III NSCLC (18, 19). Our data support these results.

The current staging system for NSCLC has served us well for a number of years. This system has helped us design a treatment plan and discuss patient prognoses. However, the

most complex and unsatisfactory aspect of the current TNM staging system is the method of assessing nodal disease. At present, mediastinal node diseases are grouped together under stage IIIA. However, there is a huge variation in the extent of N2 disease, ranging from incidental nodal metastasis to bulky multiple station, unresectable lymphadenopathy. Clearly, these variations in stage IIIA N2 disease have far-reaching implications with respect to both therapy and prognosis. Grouping all stage IIIA N2 disease into one stage is clearly inappropriate. Furthermore, we need formal recognition for a subclassification of stage IIIA N2 that considers variation. Previous proposals have called for such a change in N2 disease classification (3, 5, 6). The previous subclassifications of LN metastasis largely depended on the clinical node factor, which were then decided by the size of the LNs, but these classifications were not always correct because LN size is influenced by several inflammatory processes, such as tuberculosis and anthracosis (20, 21). In our study, clinical N2 did not have a statistical significance.

The number of metastatic mediastinal LNs is another prognostic factor that has been considered a subclassification indicator. Multiple station N2s have been accepted as one of the most important prognostic factors (14-17). In our study, multiple station N2 patients showed a significantly poor outcome. These results confirm the relevance of subclassification based on the number of lymph node stations involved. Therefore, stage IIIA N2 NSCLC patients should be classified into two basically distinct patient subgroups: single station N2 IIIA; multiple station N2 IIIA.

Furthermore, the survival outcome in the present study showed no difference between multiple station N2 IIIA and stage IIIB patients. Andre and associates (5) reported that the prognosis of clinical N2 and multiple station N2 patients with stage IIIA disease was close to the prognosis of stage IIIB disease patients. According to these results, we suggest that multiple station N2 disease should be considered similar to stage IIIB disease for predicting patient survival and therefore that multiple station N2 disease should receive a new position in the TNM staging system.

In our study, we compared multiple station N2 with stage IIIB for survival, but a better comparison might be between multiple station N2 and N3 disease as a subgroup of stage IIIB NSCLC. Pathologically proven N3 was not available in surgically resected patients because these patients are not usually indicated for surgery. In our institution, we treated only 16 patients with N3 who underwent surgery and then were proven to be N3 after the operation. Since this number of patients was not enough to compare, we included all surgically proven stage IIIB patients.

In conclusion, multiple station N2 was one of the most important single prognostic factors indicating a poor survival rate in pathological stage IIIA N2 NSCLC patients. We found no difference in survival between multiple station N2 stage IIIA and stage IIIB patients. Therefore, we

suggest that multiple station N2 disease should be considered similar to stage IIIB disease for predicting patient survival and that these criteria should receive a new position in a new TNM staging system.

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